510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K133773

B. Purpose for Submission:

To obtain a substantial equivalence determination by demonstrating acceptable performance of the Sensititre® 18-24 hour MIC or Breakpoint Susceptibility System Test System with the revised CLSI and FDA interpretive criteria (breakpoints) for meropenem and *Enterobacteriaceae*.

Also to demonstrate acceptable performance of the Sensititre® 18-24 hour MIC or Breakpoint Susceptibility System Test System with a sufficient number of meropenem resistant isolates of the *Enterobacteriaceae* family to support removal of the limitation regarding the ability of the device to detect resistance to meropenem.

C. Measurand:

Meropenem dilution range of 0.004 - 8µg/mL

D. Type of Test:

Quantitative Antimicrobial Susceptibility Test (AST), growth based fluorescence

E. Applicant:

TREK Diagnostic Systems, Inc., (part of ThermoFisher Scientific)

F. Proprietary and Established Names:

Sensititre® 18 - 24 hour MIC Susceptibility System

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   Class II

3. Product code:

   JWY – Manual Antimicrobial Test System
   LRG – Instrument for Autoreader and Interpretation of Overnight Susceptibility Systems
   LTT – Panels, Test, Susceptibility, Antimicrobial

4. Panel:

   83 - Microbiology

H. Intended Use:

1. Intended Use:

   The Sensititre® 18 – 24 hour MIC or Breakpoint Susceptibility System is an in vitro diagnostic product for clinical susceptibility testing of non-fastidious isolates.

   This 510(k) is for the removal of the limitation for the ability to detect resistance for meropenem (0.004 - 8µg/mL) and Enterobacteriaceae and for the addition of the newly approved breakpoints (S≤1, I=2, R≥4) on the Sensititre® 18 – 24 hour MIC panel for testing Gram negative isolates.

   The approved primary, "Indications for Use" and clinical significance for Enterobacteriaceae is for the following species:

   Escherichia coli
   Klebsiella pneumoniae
   Proteus mirabilis

   In vitro data, without clinical correlation is provided for:
   Aeromonas hydrophila
   Citrobacter koseri (formerly diversus)
   Citrobacter freundii
   Enterobacter cloacae
   Hafnia alvei
   Klebsiella oxytoca
   Morganella morganii
   Proteus vulgaris
   Serratia marcescens

2. Indication(s) for use:

   The Sensititre® 18 – 24 hour MIC or Breakpoint Susceptibility System is an in vitro diagnostic product for clinical susceptibility testing of non-fastidious isolates.

This 510(k) is for the removal of the limitation for the ability to detect resistance for meropenem (0.004 - 8µg/mL) and Enterobacteriaceae and for the addition of the newly approved breakpoints (S≤1, I=2, R≥4) on the Sensititre® 18 – 24 hour MIC panel for testing Gram negative isolates.

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Hafnia alvei
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Serratia marcescens

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Sensititre Autoinoculator for panel inoculation.

I. Device Description:

The Sensititre® 18-24 hour MIC or Breakpoint Susceptibility System is a micro-version of the classic broth dilution method and can provide both qualitative and quantitative susceptibility test results in a dried microtitre plate format. Each micro-broth dilution plate is dosed with antimicrobial agents as specific concentrations and then dried.

The organism to be tested must be in pure culture and identified as Gram negative. A standardized suspension is prepared from colonies in pure growth and inoculated into the microtitre plate. After the indicated hours of incubation, the microtitre plate is examined for growth to determine the MIC using either the Sensititre® Autoreader or manually using the VIZION.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Siemens' MicroScan®, Dried Gram-Negative and Gram-Positive MIC/Combo Panels

2. Predicate 510(k) number(s):

   K010159

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	In vitro diagnostic product for clinical susceptibility testing of non-fastidious (Gram negative and Gram positive organism)	Same
Isolates	Isolated colonies from culture used	Same
Sample Preparation	Inoculation density of 0.5 McFarland Standard	Same
Technology	Automated method based on fluorescence detection of growth. Manual method based on turbidity	Same
Results Reported	Report results as minimum inhibitory concentration (MIC) and interpretive criteria (SIR)	Same
Type of Test	Automated or Manual	Same

Differences		
Item	Device	Predicate
Incubation	18-24 hours	16-24 hours
Antibiotic	Meropenem	Gatifloxacin

K. Standard/Guidance Document Referenced (if applicable):

1. Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test Systems; Guidance for Industry and FDA

2. CLSI M100-S23: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-third Informational Supplement

3. CLSI M7-A9: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard- Ninth Edition

L. Test Principle:

The Sensititre® 18-24 MIC Susceptibility System test panels are multi-well plastic microtitre plates that contain doubling dilution of antibacterial agents. Each plate includes antimicrobial agents at appropriate dilutions. Results can be read manually by visual reading of growth or automatically on an autoreader via fluorescence. The Sensititre Autoreader® /OptiRead® System utilizes fluorescence technology to read the microbroth dilution plates after 18 to 24 hours incubation. The technology involves the detection of bacterial growth by monitoring the activity of specific surface enzymes produced by the test organism. Growth is determined by generating a fluorescent product from a non-fluorescent (fluorogenic) substrate. The non-fluorescent substrate is prepared by conjugating a fluorescent compound to the specific enzyme substrates with a bond which prevents fluorescence. The enzymatic action of the bacterial surface enzymes on the bound non-fluorescent substrate cleaves the bond releasing the fluorescence. The amount of fluorescence detected is directly related to the activity of bacterial growth. The MIC is determined by observing the lowest dilution of antimicrobial agent that inhibits growth of the organism. The non-fluorescent (fluorogenic) substrate can be added to the inoculum broth which is dispensed into the test plate at the same time as the test organism, or, the plates can be prepared with the substrate already added to each micro-well.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

a. Precision/Reproducibility:

Not Applicable. The scope of the submission is to re-evaluate the performance of the device using the revised CLSI and FDA meropenem breakpoints. Since there was no need for a change in the design or the dilution range on the panel, there was no need to conduct a formal clinical study or reproducibility testing. Quality control (QC) testing specific to the change in breakpoints was also not performed as QC ranges have not changed. QC testing was performed as part of the challenge study testing of meropenem resistant isolates and is described below.

b. Linearity/assay reportable range:

Not Applicable

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Quality control (QC) isolates recommended by both the FDA (CDER) and the CLSI, namely *E. coli 25922* and *P. aeruginosa 27853* were tested against meropenem each day of testing during meropenem resistant isolate challenge study. QC testing using both the broth microdilution reference method and the Sensititre® Susceptibility System test panels was performed at one site (in-house). Both manual and autoread methods of the Sensititre® test panels were used. The Sensititre® nephelometer was used to standardize the prepared inoculum, and calibrated at regular intervals.

The overall QC results for both the reference and test panels appeared to be acceptable, however it should be noted that the limited dilution range chosen for the Sensititre® test panels used in the challenge study, resulted in off-scale MIC values for both QC organisms (Table 1). The study data obtained by reference panel testing was deemed acceptable since all QC data were within the acceptable range for this method. Therefore, this data was acceptable for the purpose of performance evaluation of the Sensititre® panel.

Table 1. Quality Control - Sensititre® Susceptibility Panels

ORGANISM	Conc. (µg/mL)	Broth Microdilution Reference Method	Sensititre Autoread	Sensititre Manual
E. coli ATCC 25922 Expected Range : 0.008-0.06 µg/mL	0.004			
	0.008			
	0.015	6		
	0.03			
	0.06			
	0.12			
	0.25			
	0.5			
	≤0.5*		6	6
	1			
	2			
P. aeruginosa 27853 Expected Range : 0.25-1 µg/mL	0.12			
	0.25	6		
	0.5			
	≤0.5*		6	6
	1			
	2			

* The dilution range on the Sensititre® test panel used for testing resistant isolate challenge study did not include the full FDA/CLSI-recommended range for these QC organisms. The lowest dilution concentration of this panel was 0.5 µg/mL, therefore finite (on-scale) MIC values were not achievable.

d. Detection limit:

Not Applicable

e. Analytical specificity:

Not Applicable

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

Performance evaluation of the Sensititre® 18-24 hour MIC or Breakpoint Susceptibility System Test System with newly revised interpretive criteria (≤1, 2, ≥4) for Meropenem and *Enterobacteriaceae*.

Since there was no change in the design or the dilution range on the panel, the performance evaluation of the Sensititre® panel was achieved via re-analysis of the MIC data points of the original 510(k) submission (K983244) by using the newly revised interpretive criteria for Meropenem and *Enterobacteriaceae*. The performance evaluation included the full dilution range (0.004 - 8 µg/mL) for both the reference and device test panels.

A total of 307 non-fastidious Gram negative rods of the *Enterobacteriaceae* family (68 *E. coli*, 50 *K. pneumoniae*, 17 *S. marcescens*, 7 *E. agglomerans*, 27 *E. aerogenes*, 23 *E. cloacae*, 1 *Enterobacter spp*., 8 *C. freundii*, 4 *C. koseri*, 7 *Citrobacter spp*., 30 *P. mirabilis*, 9 *P. vulgaris*, 12 *P. rettgeri*, 12 *P. stuartii*, 1 *Providencia spp*., 14 *M. morganii*, 6 *H. alvei*, 4 *Salmonella spp*., 2 *Shigella spp*., 5 *Aeromonas spp*.) were tested. Of the 307 isolates, 227 were clinical isolates and 80 were challenge strains.

Tables 2 and 3 demonstrate performance based on essential agreement and category agreement of both clinical and challenge isolates. The data is stratified based on method of plate read (Manual or Auto).

Table 2. Non-Fastidious Gram Negatives/ Manual Read	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	%CA	#R	min	maj	vmj
Clinical	227	225	99.1	227	225	99.1	227	100	0	0	0	0
Challenge	80	80	100	80	80	100	80	100	0	0	0	0
Combined	307	305	99.3	307	305	99.3	307	100	0	0	0	0

Table 3. Non-Fastidious Gram Negatives/ Autoread	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	%CA	#R	min	maj	vmj
Clinical	226*	219	96.9	226	219	96.9	226	100	0	0	0	0
Challenge	80	79	98.8	80	79	98.8	80	100	0	0	0	0
Combined	306	298	97.4	306	298	97.4	306	100	0	0	0	0

*One isolate of Citrobacter spp. had no MIC result

EA = Essential Agreement
CA = Category Agreement
R = Resistant Isolates
min = minor discrepancies
maj = major discrepancies
vmj = very major discrepancies

Evaluable results are those that fall within the test range of the reference method and could also be on-scale with the new device if within plus/minus one dilution. Essential Agreement (EA) occurs when there is agreement between the result of the reference method and that of Sensititre test panel within plus or minus one serial two-fold dilution of the antibiotic. Category Agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre® panel result.

In each instance, both the percent Category Agreement (CA) and percent Essential Agreement (EA) consistently fall above 90%, and are therefore acceptable as described in the "Class II Special Controls guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA, August 2009". A comparative evaluation of performance data of the Manual and Autoread methods revealed very little difference. No very major, major, or minor discrepancies were observed.

Performance testing to support removal of the limitation regarding the ability of the Sensititre® 18-24 MIC Susceptibility System test panels to detect resistance to Meropenem.

An additional study was conducted to evaluate performance with resistant isolates. The CLSI broth microdilution panel was prepared according to the CLSI standard recommendation and used as the reference method. The device evaluation was performed using the Sensititre® test panel with a limited dilution range (0.5 - 8 µg/mL) and the reference panel with the full dilution range (0.004 - 8 µg/mL). The QC testing associated with this study was performed using both the reference full dilution range panel and the Sensititre® test panel with the limited dilution range for *E. coli* ATCC 25922 and *P. aeruginosa* 27853.

Performance testing was conducted in-house using 75 non-fastidious challenge isolates of the *Enterobacteriaceae* family (3 *E. coli*, 4 *E. cloacae*, 1 *Enterobacter spp*., 1 *K. oxytoca*, 63 *K. pneumoniae*, 2 *S. marcescens*, and 1 *Salmonella spp*.). A total of 62 isolates tested were found to be resistant.

The percent growth rate of this study was 100%.

Tables 4 and 5 demonstrate performance based on essential agreement and category agreement of the challenge isolates. The data is stratified based on method of plate read (Manual or Auto).

Table 4. Non-Fastidious Gram Negatives/ Manual Read	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	%CA	#R	min	maj	vmj
Challenge	75	75	100	37	37	100	72	96	62	3	0	0

Table 5. Non-Fastidious Gram Negatives/ Auto Read	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	%CA	#R	min	maj	vmj
Challenge	75	73	97.3	41	41	100	69	92	62	6	0	0

EA = Essential Agreement
CA = Category Agreement
R = Resistant Isolates
min = minor discrepancies
maj = major discrepancies
vmj = very major discrepancies

Evaluable results are those that fall within the test range of the reference method and could also be on-scale with the new device if within plus/minus one dilution. Essential Agreement (EA) occurs when there is agreement between the result of the reference method and that of Sensititre test panel within plus or minus one serial two-fold dilution of the antibiotic. Category Agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre® panel result.

In each instance, both the percent Category Agreement (CA) and percent Essential Agreement (EA) consistently fall above 90%, and are therefore acceptable as described in the "Class II Special Controls guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA, August 2009". A comparative evaluation of performance data of the Manual and Autoread methods revealed very little difference. No very major or major discrepancies were observed. The minor discrepancies which occurred all fell within Essential Agreement of the reference method result.

b. Matrix comparison:

Not Applicable

3. Clinical studies:

   a. Clinical Sensitivity:

   Not Applicable

   b. Clinical specificity:

   Not Applicable

   c. Other clinical supportive data (when a. and b. are not applicable):

   Not Applicable

4. Clinical cut-off**:**

   Not Applicable

5. Expected values/Reference range:

   Meropenem interpretive criteria for *Enterobacteriaceae*: (S≤1, I=2, R≥4)

   The appropriate recommended QC organisms were used to evaluate performance of all data.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.